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Hippocampal Atrophy in Subcortical Vascular Dementia

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Key Words
Hippocampal atrophy · Vascular dementia, subcortical

Abstract
Background and Purpose: New research criteria for subcortical vascular dementia (SVaD) have been suggested to define a more homogeneous subgroup of vascular dementia. Hippocampal (Hc) atrophy is a hallmark of Alzheimer's disease (AD), but it also occurs in other dementia disorders including vascular dementias. So far, it is unknown to which extent Hc atrophy is present in SVaD. ***Methods:*** From a larger consecutive referral population in a memory clinic, 11 patients fulfilling the research criteria for SVaD were carefully matched with comparison groups of healthy controls and patients with AD. To estimate the extent of Hc atrophy in SVaD, both Hc volumetry and visual rating of medial temporal lobe atrophy (MTA) were applied. ***Results:*** In SVaD, significant Hc atrophy occurred. The extent was intermediate between controls and patients with AD both on Hc volumetry and visual MTA ratings. At the same level of global cognition, Hc volumes were reduced by 11.6% in SVaD and 16.6% in AD, relative to controls. ***Conclusions:*** Patient groups with AD and SVaD as identified by current research criteria appear to overlap considerably with regard to the feature of Hc atrophy. While contamination with AD is a likely cause, other mechanisms of Hc atrophy in SVaD also deserve consideration. The findings have implications for the design of future clinical trials of SVaD.

Introduction

Vascular dementia is a broad term encompassing heterogeneous clinical and pathological syndromes [1]. Recognizing the need for well-defined and homogeneous subtypes of vascular dementia, new research criteria have been proposed for subcortical vascular dementia (SVaD) [2], which is presumed to be the most common type of vascular dementia. These criteria emphasize small vessel disease as the chief vascular etiology, lacunar infarcts and ischemic white matter lesions as the primary type of brain lesions, subcortical location as the primary location of the lesions, and the subcortical clinical syndrome as the primary clinical manifestation [2]. The new criteria are expected to lead to a more predictable clinical presentation, natural history, outcome and treatment responses [2].

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Hippocampal (Hc) atrophy frequently occurs in Alzheimer's disease (AD) [3–6], but also in other dementia disorders [7–9]. A number of previous studies reported evidence of significant Hc atrophy in vascular dementia [7, 9–14], and one recent study stressed the relevance of Hc atrophy regarding treatment responses in a randomized trial [15]. However, these findings have been based on heterogeneous definitions of vascular dementia and often included patients with cortical lesions. So far, it remains unclear to which extent Hc atrophy is present in SVaD.

In this study, we therefore investigated Hc atrophy on MRI in SvaD in comparison to AD and healthy control subjects. We used both Hc volumetry and visual ratings of medial temporal lobe atrophy (MTA) [5].

Methods

Subjects and Pair-Matching Procedure

The subjects were recruited from all patients and controls seen at the Free University Medical Center (VUMC) Amsterdam between January 2000 and June 2003. The new SVaD criteria [2] were operationalized in the following way: all patients had to have both (a) objective impairment of memory and executive functions (cognitive phenotype of SVaD) and (b) extending periventricular and deep white matter lesions on brain MRI (radiological phenotype of SVaD). Patients with cortical infarcts were excluded. Of all patients seen at the VUMC, 11 met these criteria for SVaD [2].

In the same time period (January 2000 to December 2003), 77 patients were diagnosed with AD according to the NINCDS research criteria and published diagnostic procedures [5]. Of those, 11 patients were selected who optimally matched the SVaD patients in age, gender and severity of cognitive impairment. Recorded results from the Mini-Mental State Examination (MMSE) [16] and the global score of the Clinical Dementia Rating (CDR) scale [17] were used to match the disease groups for severity of cognitive impairment.

Thirty-one healthy control subjects were recruited through advertisements and among spouses and friends of demented patients. They did not report any cognitive complaints. Eleven controls matching the vascular dementia patients in age and gender were chosen.

Clinical and Neuropsychological Instruments

The MMSE [16] and CDR scale [17] belong to a set of standard batteries routinely used at the VUMC. The CDR was based on information from both patients and a collateral source, and was determined according to published rules [17].

MRI Acquisition

MRI was conducted with a 1.0-tesla tomograph (Siemens Magnetom Impact Expert, Erlangen, Germany) using a magnetization-prepared rapid gradient echo (MPRAGE) and a fluid-attenuated inversion recovery (FLAIR) sequence with the following characteristics: (1) MPRAGE – coronal, TR = 15 ms, TE = 7 ms, TI = 300 ms, matrix 256 × 256, pixel dimensions 0.98 × 0.98 mm, slice thickness 1.49 mm; (2) FLAIR – axial, TR = 9,000 ms, TE = 105 ms, TI = 2,200 ms, matrix 256 × 256 × 17, pixel dimensions 0.98 × 0.98 mm, slice thickness 5.0 mm.

Hc Volumetry and Visual Ratings

To examine the occurrence and extent of Hc atrophy, both visual and volumetric assessments were performed. Both raters (L.v.d.P. and A. Hensel) were blinded to diagnosis, age and identity of the patients as well as each other's rating results.

All visual assessments were performed by L.v.d.P. Hc atrophy was visually assessed by the MTA rating scale [5]. MTA was rated on coronal MPRAGE images separately for each hemisphere. For the purpose of this study, the maximum score for either hemisphere was recorded. In addition, age-related white matter changes (ARWMC) were rated on the axial FLAIR images using the ARWMC scale [18]. Ten scans were rated twice (by L.v.d.P.) to assess intrarater reliability. The κ values were 0.7 for the MTA rating and 0.8 for the ARWMC rating.

Hc volumetry was performed by A. Hensel on the MPRAGE images using the BRIAN software package. Volumetric datasets were transferred to a UNIX system and processed as previously described [19]. Six cross-sections of the hippocampus were segmented manually in the coronal plane on both hemispheres. The left and right Hc volumes were summed to yield the total Hc volume.

All patients and controls provided written informed consent for their clinical data to be used for research. The study received ethical approval by the local ethics committee at the VU University Amsterdam.

Statistical Analyses

All statistical computations were performed using SPSS for Windows (version 12.0.0). The significance level was set to be 0.05 for all analyses. Group differences in Hc volumes as well as MTA and ARWMC scores were assessed by the Kruskal-Wallis H test, followed by groupwise comparison by Mann-Whitney U tests.

Results

The sample characteristics are summarized in table 1. Controls and disease groups were accurately matched regarding age and gender. Concerning severity of cognitive impairment and duration of symptoms, the disease groups compared well. In accordance with the diagnoses, white matter changes were significantly more pronounced in SVaD patients than in AD patients and controls.

Hc volumes were significantly reduced in both SVaD and AD – by 11.6 and 16.6%, respectively – as compared with controls (Kruskal-Wallis test; $p = 0.002$). Hc volumes in SVaD were intermediate and differed significantly from AD ($p = 0.001$) and controls ($p = 0.015$) (fig. 1). The MTA ratings confirmed this pattern (table 2). The MTA scores differed significantly between the three

Table 1. Description of the sample

	SVaD	AD	Control
Number[1]	11 (4)	11 (4)	11 (4)
Age, years	67 ± 8	69 ± 8	68 ± 8
MMSE score			
Mean ± SD	22 ± 3	22 ± 3	28 ± 2
Range	16–27	17–26	24–30
CDR score, n			
0.5	3	4	0
1	8	5	0
2	0	2	0
Symptom duration, years	3 ± 2	4 ± 3	0
Hc volume left + right, cm^3	3.20 ± 0.32	3.02 ± 0.34	3.62 ± 0.37
ARWMC rating			
Median	17	1	4
Range	7–21	0–6	5–20

Values are means ± SD unless specified otherwise. In 3 cases (2 SVaD, 1 control), the MMSE score was missing.
[1] Values in parentheses denote numbers of females.

Table 2. MTA ratings

	Number of subjects		
	control	SVaD	AD
MTA score			
0 (no atrophy)	3	0	0
1	6	2	2
2	2	5	2
3	0	3	6
4 (most severe atrophy)	0	1	1

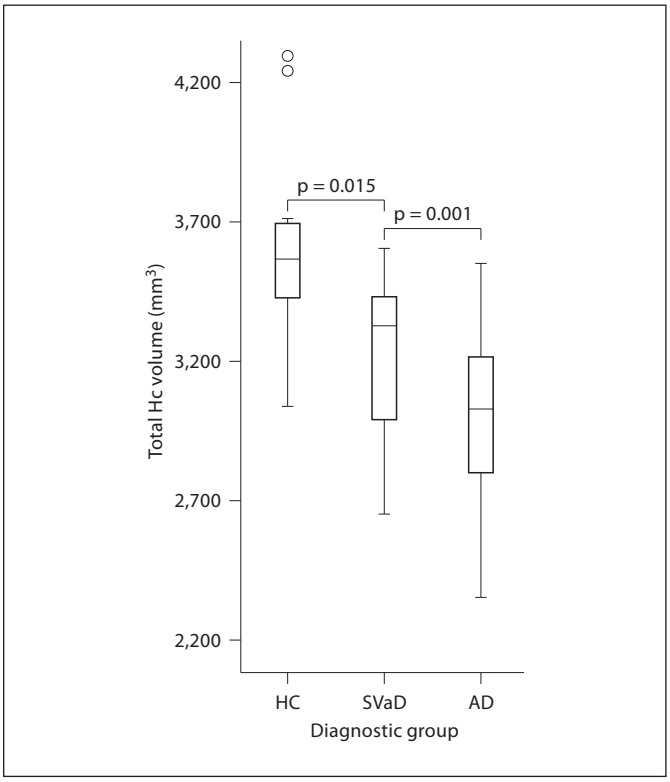

Fig. 1. Boxplot of total Hc volume estimate in patients with SVaD and AD and in healthy controls (HC; n = 33). Boxes: interquartile range. Lines in boxes: medians. Outliers are displayed individually.

groups (Kruskal-Wallis test; p = 0.001), and MTA rating scores in SVaD were intermediate between controls and AD patients, with significant differences between SVaD and controls (p = 0.002) as well as between SVaD and AD (p = 0.001). Nine SVaD as well as 9 AD patients, but only 2 controls, had MTA scores of 2 or greater. Moderate (score 3) and severe atrophy (score 4) tended to be more common in patients with AD compared with SVaD (7 vs. 4).

Discussion

To our knowledge, this is the first study to quantify Hc atrophy in stringently defined SVaD in comparison to AD and healthy controls. In contrast to other studies using heterogeneous definitions of vascular dementia, the disease groups were accurately matched for level of global cognitive impairment, age and gender.

Subjects with SVaD had significant Hc atrophy, evident by both Hc volumetry and visual rating of MTA scores as compared with controls. While MTA and Hc volume reductions in SVaD occurred with a comparable frequency to AD, Hc atrophy was significantly less severe than in AD. These findings are comparable with a number of previous studies showing that Hc atrophy commonly occurs in vascular dementia [7, 9–13] and might be milder than in AD [7, 9, 11]. However, none of these studies strictly focused on SVaD.

The mechanisms of Hc atrophy in SVaD remain unclear and could be heterogeneous. One possible explanation for our findings is that cooccurrent Alzheimer pathology, particularly neurofibrillary tangles (NFT), may have contributed to the Hc atrophy seen in SVaD. Close

correlations have been shown between Hc neuronal loss, NFT and Hc atrophy in cases with AD [20], and even across different dementia disorders [10].

However, Hc atrophy in SVaD has been shown to occur in the absence of AD pathology. In postmortem studies, up to 50% of cases with SVaD were found to have Braak stages of 0/I, i.e. negligible NFT pathology [20–22]. Yet, there was significant Hc pyramidal cell loss in some of these cases [21]. The most important findings in support of 'pure' vascular mechanisms of Hc atrophy derive from cases with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). These patients often have pronounced Hc atrophy correlating with their global cognitive state, but because they are aged <60 years, comorbid Alzheimer pathology is unlikely [23].

In a large histopathological case series of ischemic vascular dementia, some manner of Hc injury was commonly found and the substrates were noted to be extremely variable, ranging from regions with cystic encephalomalacia to well-defined regions with segmental Hc scarring, resembling Hc sclerosis [22].

In our sample, patients with SVaD had significantly less Hc atrophy despite the same degree of global cognitive disturbances as AD patients (MMSE score 22), but the quantitative difference was small (5%). Larger studies on vascular dementia add plausibility to this finding by showing that Hc atrophy is the major correlate of global cognition in vascular dementia, whereas white matter lesions contribute more specifically to executive dysfunction [24]. Beyond easily detectable radiological phenomena of white matter lesions and Hc atrophy, the cholinergic denervation caused by ischemic damage to fiber tracts appears to be of specific pathophysiological relevance in SVaD [25]. Differing pathophysiological mechanisms (neurodegenerative vs. microvascular) could result in shape and texture differences, possibly leading to small but significant differences in Hc volume between AD and SVaD. This needs to be addressed in future imaging studies.

Some limitations of our study have to be mentioned. The sample size was small, but the design was optimized to create homogeneous groups and to avoid the use of statistical corrections. It remains unclear whether the volumetric estimations from our study can be generalized. The Hc volume loss in the AD group was rather small compared with other studies, some of which used the same protocol [19, 26]. This could be due to the relatively young age, mild disease severity or chance. A smaller than expected Hc volume loss in AD decreases the power to detect a true group difference, and hence also the likelihood of a type I error.

In conclusion, patient groups with AD and SVaD as identified by current research criteria appear to overlap considerably with regard to the feature of Hc atrophy. While contamination with AD is a likely cause, other mechanisms of Hc atrophy in SVaD also deserve consideration. In future trials of SVaD, the degree of Hc atrophy should be taken into account in addition to the defining features.

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